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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/827,289	04/05/2001	Patricio Abarzua	469290-55	5725

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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT

PAPER NUMBER

1634

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/827,289	ABARZUA, PATRICIO	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31-50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 31 is/are allowed.
- 6) ☒ Claim(s) 32-40 and 42-50 is/are rejected.
- 7) ☒ Claim(s) 41 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>11</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 6, 2003 has been entered.

Status

2. Any rejection not reiterated in this action is hereby withdrawn.

Claims 31-50 are pending. Claim 31 is allowed. Claims 32-40, 42-50 are rejected. Claim 41 is objected to.

Claim Rejections - 35 USC § 112

3. The rejection under 35 U.S.C 112, second paragraph is withdrawn in view of the amendment.

Claim Objections

4. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 39-51 been renumbered 38-50. In particular, it appears that there is no claim 38 in the new amendment. Therefore, the claims after claim 37 were renumbered to correct this inadvertent error.

Claim Interpretation

5. In claim 32, step (a), the claim notes that "the terminal nucleotide and the third nucleotide from the terminal nucleotide, at said one end of said p1 may independently be non-complementary to the corresponding nucleotide". The use of the word "may" indicates that this element is optional for claim 32, and that the nucleotides may be either complementary or non-complementary.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 32-40, 42-46, and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Lizardi et al (Nature Genetics (1998) 19:225-232).

Lizardi teaches a method of detecting single nucleotide polymorphisms (alleles) (see abstract and page 226) comprising:

(a) contacting an allele specific oligonucleotide primer with a target polynucleotide, wherein the target polynucleotide has a first portion which is complementary to a second portion on the allele specific oligonucleotide primer under

conditions which permit hybridization between the two portions (page 226 and figure 2, panel C, where a padlock primer hybridizes to the target during PCR),

(b) contacting the complex of primer and target nucleic acids with an exonuclease deficient DNA polymerase which extends the primer (see page 226, figure 2, panel C and figure legend and page 231, subheading "Probe ligations using gap oligonucleotides or gap-filling") where the polymerase is *Thermus flavus* DNA polymerase (see page 226, column 1) which lacks 3'-5' exonuclease activity, and where extension occurs by the polymerase only when the terminal nucleotide of the primer is complementary to the corresponding nucleotide of the target (see page 226, columns 1 and 2 and figure 2, panel C)

(c) determining the extended primer by removing the target polynucleotide from the complex formed in step (b) (which occurs since the primer is no longer hybridized to the target as shown in figure 1, panel C) and contacting the extended primer with a second oligonucleotide which hybridizes to a region of the extended primer which was not in the original primer region under conditions which permit rolling circle replication (see page 227, figure 4) whereby "TS-DNA" is formed that indicates the presence of the polymorphism in the target (see page 226, column 2 and figure 5, panel A).

With regard to claim 33, Lizardi teaches the use of primers with a 3'-5'-3' polarity (see page 228, figure 6) in the RCA method taught by Chee (see page 228).

With regard to claims 34-35, Lizardi teaches detection in human genomic samples (see page 229, figure 8, for example).

With regard to claim 36, Lizardi teaches detection of an artificial target (see page 226, figure 2).

With regard to claim 37, Lizardi teaches the use of sequenase (see page 230, column 1).

With regard to claims 38-40, Lizardi teaches detection using RCA on solid supports such as immobilization on glass slides (see page 231, column 2).

With regard to claims 42-46, Lizardi teaches detection of a G542X locus mutation of CFTR (see page 225, column 1).

With regard to claim 48, Lizardi teaches the third nucleotide from the end of P1 is complementary to the target (see figure 2).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 32, 34-40 and 42-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valimaa et al (J. Immunol. Methods (1998) 219:131-137) in view of Chee et al (U.S. Patent 6,355,431).

Valimaa teaches a method of detecting single nucleotide polymorphisms (alleles) (abstract) comprising:

(a) contacting an allele specific oligonucleotide primer with a target polynucleotide, wherein the target polynucleotide has a first portion which is complementary to a second portion on the allele specific oligonucleotide primer under conditions which permit hybridization between the two portions (page 133, column 1, subheading "PCR", where the allele specific primer hybridizes to the target during PCR),

(b) contacting the complex of primer and target nucleic acids with an exonuclease deficient DNA polymerase which extends the primer (see page 133, column 1, subheading "PCR") where the polymerase is Dynazyme II which lacks 3'-5' exonuclease activity only when the terminal nucleotide of the primer is complementary to the corresponding nucleotide of the target (see page 133, column 1, subheading "PCR")

(c) detecting the extended primer (here a PCR product) by removing the target polynucleotide from the complex formed in step (b) by attaching the primer to a solid support composed of plastic (see page 133, subheading "hybridization") and contacting the extended primer (here the PCR product) with a second oligonucleotide which hybridizes to a region of the extended primer (PCR product) which was not in the original primer region (see page 133, column 2, subheading "hybridization"),

(d) detecting the hybridization of the second oligonucleotide with the extended primer whereby said hybridization indicates extension of the primer thereby detecting a polymorphism in the target polynucleotide (see page 133, column 2 and page 135, figure 2).

With regard to claims 34-35, Valimaa teaches the use of samples taken directly from human blood which would comprise human genomic DNA.

With regard to claims 38-40, Valimaa teaches attaching the primer to a solid support composed of plastic (see page 133, subheading "hybridization").

Valimaa teaches the use of an exonuclease deficient polymerase but not the full list given by Chee. Valimaa does not teach detection using rolling circle amplification.

Chee teaches the desirability of detecting single nucleotide polymorphisms (column 16, lines 25-64) including the use of Klenow, Sequenase, T5 DNA polymerase and Phi29 DNA polymerase among others (column 17, lines 10-12). Chee further teaches detection of the single base extended product using rolling circle amplification with an additional primer that forms a circle (see columns 19-22).

Chee further teaches detection of target sequences in cancer (see column 56, lines 25-29) as well a detection of human clinical samples (which would contain human genomic DNA) for HIV (which would have HIV genomic DNA) (see column 56, lines 35-47).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Valimaa, which is a method in which a mutation is detected by hybridization to a probe with a label, by using the method of Chee who teaches detection of single base extension using a probe with a label where the label enables rolling circle amplification, since the rolling circle amplification of Chee will very significantly increase the signal, making the method of Valimaa more sensitive and more accurate. As Chee notes,

"The RCA as described herein finds use in allowing highly specific and highly sensitive detection of nucleic acid target sequences. In particular, the method finds use in improving the multiplexing ability of DNA arrays and eliminating costly sample or target preparation. As an example, a substantial savings in cost can be realized by directly analyzing genomic DNA on an array, rather than employing an intermediate PCR amplification step. The method finds use in examining genomic DNA and other samples including mRNA. In addition the RCA finds use in allowing rolling circle amplification products to be easily detected by hybridization to probes in a solid-phase format (e.g. an array of beads). An additional advantage of the RCA is that it provides the capability of multiplex analysis so that large numbers of sequences can be analyzed in parallel. By combining the sensitivity of RCA and parallel detection on arrays, many sequences can be analyzed directly from genomic DNA. (column 22, lines 42-59)".

Thus, an ordinary practitioner would have been motivated to use RCA as a detectable label in the method of Valimaa since RCA saves money, permits multiplexing, increases sensitivity and permits direct detection of genomic DNA.

10. Claims 32-40, 42-46, and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al (Nature Genetics (1998) 19:225-232) in view of Ishikawa et al (Human Immunology (1995) 42:315-318).

Lizardi teaches a method of detecting single nucleotide polymorphisms (alleles) (see abstract and page 226) comprising:

(a) contacting an allele specific oligonucleotide primer with a target polynucleotide, wherein the target polynucleotide has a first portion which is

complementary to a second portion on the allele specific oligonucleotide primer under conditions which permit hybridization between the two portions (page 226 and figure 2, panel C, where a padlock primer hybridizes to the target during PCR),

(b) contacting the complex of primer and target nucleic acids with an exonuclease deficient DNA polymerase which extends the primer (see page 226, figure 2, panel C and figure legend and page 231, subheading "Probe ligations using gap oligonucleotides or gap-filling") where the polymerase is *Thermus flavus* DNA polymerase (see page 226, column 1) which lacks 3'-5' exonuclease activity, and where extension occurs by the polymerase only when the terminal nucleotide of the primer is complementary to the corresponding nucleotide of the target (see page 226, columns 1 and 2 and figure 2, panel C)

(c) determining the extended primer by removing the target polynucleotide from the complex formed in step (b) (which occurs since the primer is no longer hybridized to the target as shown in figure 1, panel C) and contacting the extended primer with a second oligonucleotide which hybridizes to a region of the extended primer which was not in the original primer region under conditions which permit rolling circle replication (see page 227, figure 4) whereby "TS-DNA" is formed that indicates the presence of the polymorphism in the target (see page 226, column 2 and figure 5, panel A).

With regard to claim 33, Lizardi teaches the use of primers with a 3'-5'-3' polarity (see page 228, figure 6) in the RCA method taught by Chee (see page 228).

With regard to claims 34-35, Lizardi teaches detection in human genomic samples (see page 229, figure 8, for example).

With regard to claim 36, Lizardi teaches detection of an artificial target (see page 226, figure 2).

With regard to claim 37, Lizardi teaches the use of sequenase (see page 230, column 1).

With regard to claims 38-40, Lizardi teaches detection using RCA on solid supports such as immobilization on glass slides (see page 231, column 2).

With regard to claims 42-46, Lizardi teaches detection of a G542X locus mutation of CFTR (see page 225, column 1).

With regard to claim 48, Lizardi teaches the third nucleotide from the end of P1 is complementary to the target (see figure 2).

Lizardi does not teach the use of primers with mismatches near the 3' termini.

Ishikawa teaches that putting mismatches in primers near the 3' termini increases the specificity of amplification (abstract and page 316, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Lizardi for allele specific amplification to use primers which have been modified to improve specificity as taught by Ishikawa since Ishikawa states "the introduction of an additional one-base mismatch is a simple and useful way to improve the specificity (page 316, column 2)". An ordinary practitioner would have been motivated to modify the primers of Valimaa in view of Chee by creating mismatches near the 3' end in order to improve the specificity of the single base extension reaction, thereby improving the quality of the assay and reducing the number of false negative and false positives which would otherwise occur.

11. Claims 32, 34-40 and 42-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valimaa et al (J. Immunol. Methods (1998) 219:131-137) in view of Chee et al (U.S. Patent 6,355,431) and further in view of Ishikawa et al (Human Immunology (1995) 42:315-318).

Valimaa in view of Chee teach the limitations of claims 32, 34-40 and 42-48 as discussed above. Valimaa in view of Chee do not teach the use of primers with mismatches near the 3' termini.

Ishikawa teaches that putting mismatches in primers near the 3' termini increases the specificity of amplification (abstract and page 316, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Valimaa in view of Chee for allele specific amplification to use primers which have been modified to improve specificity as taught by Ishikawa since Ishikawa states "the introduction of an additional one-base mismatch is a simple and useful way to improve the specificity (page 316, column 2)". An ordinary practitioner would have been motivated to modify the primers of Valimaa in view of Chee by creating mismatches near the 3' end in order to improve the specificity of the single base extension reaction, thereby improving the quality of the assay and reducing the number of false negative and false positives which would otherwise occur.

12. Claims 32-40 and 42-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valimaa et al (J. Immunol. Methods (1998) 219:131-137) in view of Chee et al (U.S. Patent 6,355,431) and further in view of Lizardi et al (Nature Genetics

(1998) 19:225-232) and further in view of Ishikawa et al (Human Immunology (1995) 42:315-318).

Valimaa in view of Chee and further in view of Ishikawa teach the limitations of claims 32, 34-40 and 42-50 as discussed above. Valimaa in view of Chee and further in view of Ishikawa do not teach primers with a 3'-5'-3' polarity.

Lizardi teaches the use of primers with a 3'-5'-3' polarity (see page 228, figure 6) in the RCA method taught by Chee (see page 228).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Valimaa in view of Chee and further in view of Ishikawa to use the 3'-5'-3' polarity primer of Lizardi since Lizardi notes "A larger range of labeling combinations is attainable by RCA-CACHET.(see page 230, column 2)." Lizardi further notes "The single molecule counting approach promises to be both sensitive and linear in its response to target concentration. Individual immunoglobulins can tagged with rolling circle primers can be detected by RCA-CACHET (see page 230, column 2)". Thus, an ordinary practitioner, motivated by Chee as discussed above to apply the RCA method, would have been further motivated by Lizardi to use the modified RCA-CACHET method in order to use a larger range of labeling combinations and increase sensitivity to the point that single molecules may be detectable.

13. Claims 32-40 and 42-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al (Nature Genetics (1998) 19:225-232) in view of Chee et al (U.S. Patent 6,355,431).

Lizardi teaches the limitations of claims 32-40, 42-46, and 48 as discussed above. Lizardi does not teach detection of cancer.

Chee et al (U.S. Patent 6,355,431) teaches detection of target sequences in cancer (see column 56, lines 25-29).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Lizardi to detect cancer as taught by Chee, since Lizardi states that the method can detect "point mutations in small amounts of human genomic DNA in solution (see page 225, column 1) and since Chee notes a desire to "detect target sequences such as the gene for nonpolyposis colon cancer, the BRCA1 breast cancer gene, P53, which is a gene associated with a variety of cancers (see column 56, lines 25-29)." Thus, an ordinary practitioner would have been motivated to use the method of Lizardi to detect cancer as taught by Chee since the method of Lizardi can detect point mutations in small amounts of human genomic DNA, permitting small biopsies of breast cancer to be tested for mutations in genes such as BRCA1 or p53 that are known to be associated with cancer.

Allowable Subject Matter

1. The elected Restriction subgroup, SEQ ID NO: 13, is novel and unobvious over the cited prior art. While the targeting region to cystic fibrosis is known, the particular sequence with the particular number of T residues attached is not taught by the prior art and is not obvious. Claim 41 is objected to as dependent from a rejected claim but if it was limited to the elected subgroup and rewritten in independent form, the claims would be allowable.

2. Claim 31 is allowed.
3. The following is a statement of reasons for the indication of allowable subject matter: Claim 31 is drawn to an embodiment of the invention which requires the use of SEQ ID NO: 13, which is novel and unobvious over the cited prior art.

Response to Arguments

4. Applicant's arguments filed August 6, 2003 have been fully considered but they are not persuasive.

Applicant argues that the rejection of Valimaa in view of Chee lacks any discussion of how the references would be combined. This argument is not persuasive since the rejection makes clear that Chee teaches that RCA is a common detection format that can be applied to any of a variety of assays. The combination simply requires the use of RCA as the detection method rather than the standard detection techniques used by Valimaa.

Applicant then argues that the claimed method does not require ligation while the method of Valimaa in view of Chee (and the newly cited 102 over Lizardi), both require ligation. There is no step in the claims which excludes ligation. The claim uses the term "comprising". As MPEP 2111.03 notes "The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps." Therefore, no limitation from the specification will be read into the claims.

Applicant then argues that there is no motivation to combine Ishikawa. This argument is not found persuasive because Ishikawa expressly teaches that the use of

mismatches will increase specificity. The increase in specificity is the same whether it occurs during PCR, primer extension, or even ligation. Thus, this argument fails to recognize that the teaching of Ishikawa is that any of the mismatches will enhance specificity in hybridization dependent assays. The fact that Ishikawa exemplifies PCR does not limit the teaching.


Applicant then reiterates, with regard to the rejection further involving Lizardi, the argument that ligation is not necessary. The claim includes no such limitation as discussed above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


Jeffrey Fredman
Primary Examiner
Art Unit 1634